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Low vitamin D levels increase the risk of type 2 diabetes in older adults: A systematic review and meta-analysis

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Highlights

- This is the first meta-analysis to investigate the relationship between vitamin D and diabetes in older adults.
- The meta-analysis included 28,258 older adults, followed for over 7.7 years.
- Lower levels of vitamin D were associated with a 31% higher risk of future diabetes
- After adjusting for 11 confounders, the risk of diabetes was 16% higher among older adults with low levels of vitamin D.

ABSTRACT

Low serum levels of 25 hydroxyvitamin D (25OHD) (hypovitaminosis D) is common in older adults and associated with several negative outcomes. The association between hypovitaminosis D and diabetes in older adults is equivocal, however. We conducted a meta-analysis investigating if hypovitaminosis D is associated with diabetes in prospective studies among older participants. Two investigators systematically searched major electronic databases, from inception until 10/07/2016. The cumulative incidence of diabetes among groups was estimated according to serum 25OHD levels. Random effect models were used to assess the association between hypovitaminosis D and diabetes at follow-up. From 4,268 non-duplicate hits, 9 studies were included; these followed 28,258 participants with a mean age of 67.7 years for a median of 7.7 years. Compared with higher levels of 25OHD, lower levels of 25OHD were associated with a higher risk of developing diabetes (6 studies; n= 13,563; RR=1.31; 95% CI: 1.11-1.54; $I^2=37\%$). The findings remained significant after adjusting for a median of 11 potential confounders in all the studies available (9 studies; n=28,258; RR=1.17; 95% CI: 1.03-1.33; p=0.02; $I^2=0\%$). In conclusion, our data suggest that hypovitaminosis D is associated with an elevated risk of future diabetes in older people. Future

longitudinal studies are required and should seek to confirm these findings and explore potential pathophysiological underpinnings.

Keywords: vitamin D; hypovitaminosis D, diabetes; aged; meta-analysis.

INTRODUCTION

Type two diabetes is one of the most prevalent and disabling conditions in older people.¹ More than 40% of all cases of diabetes are diagnosed in older adults (aged > 60 years) and the number of older people with diabetes is expected to dramatically increase in the next 20 years.² Diabetes is associated with a wide range of adverse outcomes such as pain, lower limb amputation, increased healthcare costs³, falls⁴ and cognitive decline.⁵ Although treatments for diabetes have improved, the prevention of this condition is of importance. Several potential reversible/modifiable risk factors for diabetes (including obesity, sedentary lifestyle, high blood pressure and blood cholesterol levels) are common targets for the prevention of diabetes.⁶ However, successful treatment of these risk factors has been mixed, with minimal data specifically in older adults⁷, suggesting there may be other potential risk factors that could be treatment targets.

Low vitamin D levels are a potential and easy reversible target for diabetes in older adults. Hypovitaminosis D (usually defined as low circulating serum 25 hydroxyvitamin D [25OHD] levels) is a common condition in older people.^{8–10} A number of cross-sectional and case-control studies in older adults have reported there is not a significant association between hypovitaminosis D and the presence of diabetes, particularly after adjusting the analyses for the presence of some potential confounders such as obesity.^{11–14} In contrast to younger populations, the depletion of susceptible effects might play an important part in the lack of the association between hypovitaminosis D and diabetes.¹⁵ People with low 25OHD levels in old age may be less prone to

the health hazards relating to hypovitaminosis D than those with low 25OHD levels who developed diabetes when they were younger.¹⁵ However, a large meta-analysis involving 21 prospective studies and 76,220 participants, found that having higher serum 25OHD levels protected against the onset of diabetes.¹⁶ Unfortunately, this meta-analysis included only three studies concerning older people, and all these studies reported a non-significant association between baseline serum 25OHD status and incident diabetes.¹⁶

Understanding whether hypovitaminosis D is associated with the future onset of diabetes in older adults is of importance, due to the high presence of this condition and since the reversibility of this condition is potentially very easy to address. Given this background, we conducted a systematic review and meta-analysis investigating whether low serum 25OHD (hypovitaminosis D) can predict the onset of diabetes in prospective studies among older adults.

METHODS

This systematic review was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology [STROBE] criteria¹⁷ and the recommendations in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] statement.¹⁸

Search strategy

Two independent authors (NV, MS) searched for longitudinal studies considering serum 25OHD and diabetes in older people. Major databases (PubMed, EMBASE, SCOPUS) were searched from inception until 10th July 2016, without language restrictions. The search strategy used in Pubmed was: (vitamin D OR 25-hydroxy vitamin D OR calcidiol OR calcitriol OR calcifediol) AND (insulin OR glucose OR beta-cell function OR diabetes*) AND (old OR elderly OR older OR aged) A similar search (adapted to the requirements of each database) was conducted in the other databases.

Eligibility criteria and study selection

Articles were eligible if: (1) were longitudinal prospective studies; (2) assessed serum 25OHD as indicator of vitamin D status, since it seems the best indicator for vitamin D status¹⁹; (3) included only older people, as mean age of the population ≥ 60 years; (4) reported a diagnosis of diabetes at follow-up using self-reported data, medical/hospital records, or at least one criterion suggested by the American Diabetes Association²⁰ (i.e. fasting plasma glucose (FPG) ≥ 126 mg/dl, glycosylated hemoglobin (HbA1c) $\geq 6.5\%$ or use of anti-diabetic medications). Studies were excluded if they: (1) had a cross-sectional design (2) assessed vitamin D status with methods other than serum 25OHD (e.g. dietary vitamin D); (3) included only sub-clinical estimates of diabetes (e.g. changes in fasting plasma glucose).

References of included articles included were hand-searched to identify additional, potentially relevant publications. Conference abstracts were also considered, and in such instances we contacted the corresponding authors to acquire the data to enable inclusion.

Data extraction

Two authors (AB, PL) independently recorded data extracted from the selected studies into a standardized Microsoft Excel spreadsheet. Any disagreement was resolved by consensus with a third author (BS). The following information was extracted for each study: i) study characteristics (e.g. sample size, demographics, country in which the study was performed); ii) study setting; iii) number of diabetic people during follow-up; iv) follow-up (in years); v) serum 25OHD levels and methods of assessment of 25OHD; vi) diagnostic criteria used for the diagnosis of diabetes; vii) number and type of covariates used in the multivariate analyses.

If more than two categories for serum 25OHD were included, we defined as low the lowest quantile and used the highest one as the reference group.

Assessment of study quality

Study quality was assessed by two investigators (MS, GB), while another one was available for mediation (NV). The Newcastle-Ottawa Scale (NOS)²¹ was used to assess study quality. The NOS assigns a maximum of 9 points based on three quality parameters: selection, comparability, and outcome.²¹

Statistical analysis

A random effects meta-analysis was undertaken using Comprehensive Meta-Analysis (CMA) version 3 to account for the anticipated heterogeneity.²² In the primary analyses, pooled RRs and 95% CI (including the number of incident cases of diabetes in low serum 25OHD vs. higher values) were calculated to synthesize data. In the secondary analyses, we included the HR/OR adjusted for

the highest number of covariates available for each study and analyzed together using fully-adjusted RRs.

Study heterogeneity was assessed using the chi-squared and I-squared statistics, assuming that a $p < 0.05$ for the former and a value $\geq 50\%$ for the latter indicated a significant heterogeneity.²³ Whenever significant heterogeneity existed and ≥ 4 studies were available, a meta-regression analysis was pre-planned taking as potential moderators: continent in which the study was performed, study setting (community vs. others), follow-up (as continuous, in years), diagnostic criteria used for the diagnosis of diabetes (self-reported vs. others), and number of covariates.

Publication bias was assessed by visually inspection of funnel plots and using the Egger bias test.²⁴ When ≥ 3 studies were available, we used the Duval and Tweedie nonparametric trim-and-fill method to account for potential publication bias. Based on the assumption that the effect sizes of all the studies are normally distributed around the center of a funnel plot, in the event of asymmetries, this procedure adjusts for the potential effect of unpublished (trimmed) studies.²⁴

RESULTS

The search identified 4,268 non-duplicated, potentially eligible studies. After excluding 4,229 papers on the grounds of a review of their titles and abstracts, 39 full-text articles were examined. Of the full texts, 30 were excluded (mainly being cross-sectional studies) and 9 articles^{25–33} were finally included in our meta-analysis (**Supplementary Material S1**).

Study and patient characteristics

As reported in **Table 1**, the 9 studies^{25–33} followed-up 28,258 older participants for a median follow-up period of 7.3 (range: 2–11) years in which 2,863 participants (=10.1% of the baseline population) developed diabetes.

The mean age of the participants was 67.7 ± 4.3 years and the majority were women (64%). All the studies were done among community-dwellers and mainly in Europe (studies=4) and North America (studies=4).

As reported in **Table 1**, the majority of the studies used radioimmunoassay (RIA) method for measuring 25OHD, whilst only one²⁹ chemiluminescence that is considered the gold standard for assessing serum 25OHD levels.¹⁹ Regarding the diagnosis of diabetes, two studies^{30,32} used only self-reported information. Other studies used self-reported information, but with a final adjudication by a specialist in one study²⁵, with a value of FPG over 126 mg/d in another one²⁷, and with use of anti-diabetic medications in a third study.²⁹ Two studies used a value of HbA1c over 6.5% for the diagnosis of type 2 diabetes^{26,31}, one only a value of FPG over 126 mg/dl²⁸ and finally one³³ all the criteria suggested by the American Diabetes Association.²⁰

The quality of the studies was generally of moderate quality as shown by the median eNOS values (median=7; range: 5–9) (**Table 1**).

Unadjusted findings regarding lower 25OHD levels and diabetes

As shown in **Figure 1**, 568 older participants from 5,366 with lower vs. 752/8,197 with higher serum 25OHD levels (=10.6% vs. 9.2%) had a diagnosis of diabetes during follow-up period. Lower 25OHD levels at baseline were associated with a higher risk developing diabetes compared to older people with higher 25OHD levels (6 studies ^{25,28,30–33}; n=13,563 ; RR=1.31; 95%CI: 1.11-1.54; p=0.001; I²=37%).

No publication bias was found (Egger's test=-0.28; p=0.82) and the trim and fill analysis did not change our results.

Adjusted analyses regarding lower 25OHD levels and diabetes

Figure 2 shows the association between lower serum 25OHD levels at the baseline and the onset of diabetes at follow-up after adjusting for potential confounders. The median number of adjustments in the multivariate analyses was 11 (range: 4-17), with all the studies including adiposity estimates, as shown in **Table 1**.

In the nine studies^{25–33} included (n=28,258) older participants, we observed that lower 25OHD levels at the baseline increased the risk of future diabetes of 17% (HR=1.17; 95%CI: 1.03-1.33; p=0.02; I²=0%). Publication bias was not present (Egger's test=-0.34; p=0.58) and the trim and fill analysis did not change our findings.

Meta-regression analysis

Among the outcomes included in our analyses, no one was affected by high heterogeneity and so meta-regression analyses were run.

DISCUSSION

In this meta-analysis including a total of 9 longitudinal studies and 28,258 older participants, we found evidence that hypovitaminosis D at the baseline was associated with incident diabetes at follow-up, also after adjusting for potential confounders.

It is noteworthy that on their own, none of the longitudinal studies reported a significant association between hypovitaminosis D at baseline and incident diabetes after adjusting for the presence of potential confounders. On the contrary, when we merged the data in a meta-analysis considering a median of 11 potential confounders the presence of hypovitaminosis D at baseline increased the risk of diabetes at follow-up by 17%. Altogether these findings suggest that hypovitaminosis D in older adults may be a potential risk factor for diabetes.

Previous literature, on the contrary, has suggested that hypovitaminosis D is not associated with the onset of diabetes in older adults, which may be due to a number of reasons. First, we could hypothesize that hypovitaminosis D may be a stronger predictor of mortality than diabetes in older people, as shown by a number of papers on this issue.^{34–37} Consequently, one hypothesis is that subjects with low serum 25OHD may die before developing diabetes. This hypothesis is somewhat reinforced by our meta-analysis suggesting that probably single studies do not have sufficient power to detect the association between hypovitaminosis D and diabetes, potentially due to the competitive risk of mortality. Second, several conditions are commonly associated with both hypovitaminosis D and/or diabetes. In the elderly, adiposity seems to be the most important in explaining why low 25OHD levels are not associated with diabetes in older people.¹³ This hypothesis is supported by some of the previously-mentioned studies, which found that the significant association identified between poor vitamin D status and diabetes disappeared after controlling for BMI or other adiposity measures.^{28,30} Altogether our findings are in agreement with the two previous meta-analyses^{16,38} in the general population including adults of all ages. Thus, our meta-analysis confirms for the first time that hypovitaminosis D is associated with diabetes in the elderly.

Our findings open the question whether or not supplementation with vitamin D could prevent or slow the progression of diabetes older subjects. To the best of our knowledge, only two RCTs have considered vitamin D supplementation in older individuals at higher risk of diabetes.^{39,40} It appears across these studies that oral vitamin D supplementation has no effect on glucose parameters in participants at higher risk of diabetes.^{39,40} The quality of these studies seems to be adequate, the doses of cholecalciferol used were 700 IU/day or more, and the follow-up was long enough for any significant changes to emerge in the metabolic parameters investigated.⁴¹ Based also on our results, however, future trials are needed to confirm these findings.

The findings of our study should be interpreted within its limitations. First, the observational nature of the studies included does not enable us to elucidate potential pathways responsible of the association between hypovitaminosis D and diabetes. Second, although the analyses made through HRs suggest a significant association between low serum 25OHD and diabetes, those made through adjusted ORs did not. The latter may be due to the fact only 3 study estimates were included with a more limited sample size. Third, the mean age of the subjects included is about 67 years. More focused investigations regarding very old people are so needed to better understand this association. Fourth, no gender separated analyses were run (due to the limited number of studies in each gender), even if both serum 25OHD and diabetes are usually different between men and women. Finally, serum 25OHD was mainly measured with RIA that seems to be a worse method to measure serum 25OHD than chemiluminescence.¹⁹ On the contrary, among the strengths of our work, we can include the large number of subjects included, the number of covariates used in the adjusted analyses, the follow-up period (median=7.3), long if referred to older subjects and the low heterogeneity found in almost all of the outcomes included.

CONCLUSION

Our meta-analysis suggests that hypovitaminosis D is associated with the onset of diabetes in older people after adjusting for other potential risk factors. Since hypovitaminosis D is one of the most frequent conditions in older adults and a paucity of trials have attempted to investigate whether vitamin D supplementation can prevent diabetes, future larger scale studies are needed to confirm if the supplementation with vitamin D could prevent diabetes' developing in older adults.

Contributors

PL was responsible for the concept and design of the review, the acquisition of data, and the analysis and interpretation of data, and for the preparation of the manuscript.

MS was responsible for the acquisition of data, and for the preparation of the manuscript.

SM was responsible for the analysis and interpretation of data, and for the preparation of the manuscript.

AB was responsible for the acquisition of data, and for the preparation of the manuscript.

GB was responsible for the preparation of the manuscript.

CT was responsible for the concept and design of the review, and for the preparation of the manuscript.

EM was responsible for the analysis and interpretation of data, and for the preparation of the manuscript.

GS was responsible for the preparation of the manuscript.

PS was responsible for the preparation of the manuscript.

YK was responsible for the preparation of the manuscript.

NV was responsible for the concept and design of the review, and the analysis and interpretation of data, and for the preparation of the manuscript.

BS was responsible for the concept and design of the review, the analysis and interpretation of data, and the preparation of the manuscript.

All authors saw and approved the final version of the manuscript.

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Conflict of interest

The authors declare that they have no conflict of interest.

Provenance and peer review

This article has undergone peer review.

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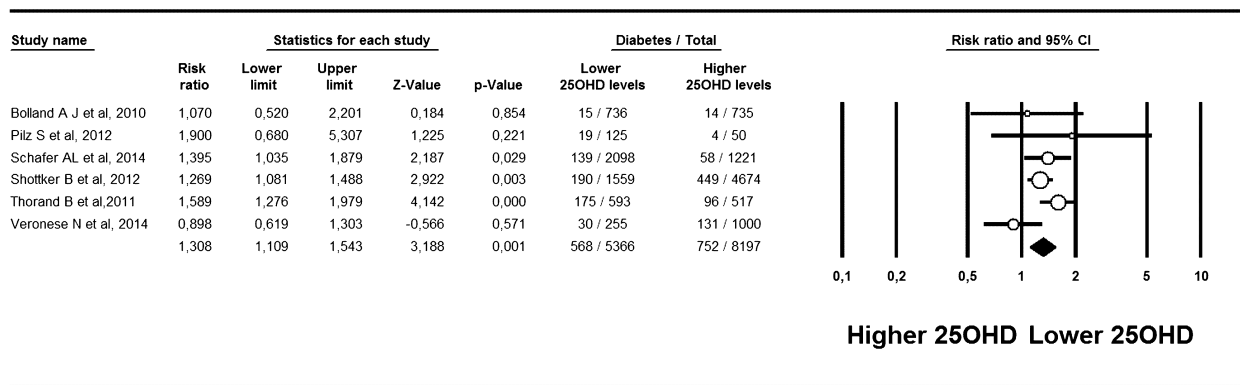
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LEGEND

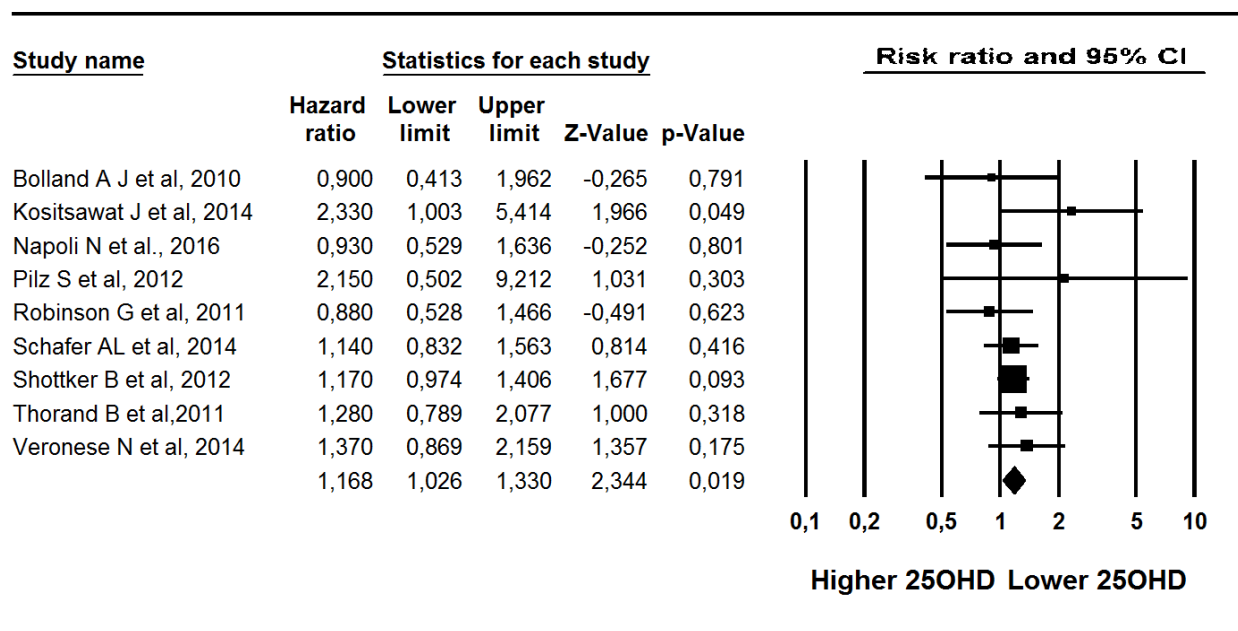
Figure 1. Association between lower 25 hydroxyvitamin D (25OHD) levels at baseline and incident diabetes.



Abbreviations: 25OHD = 25-Hydroxyvitamin D, CI = confidence interval

Figure 2. Association between lower 25 hydroxyvitamin D (25OHD) levels at baseline and incident diabetes, after adjusting for potential confounders.

Abbreviations: 25OHD = 25-Hydroxyvitamin D, CI = confidence interval.



Supplementary Figure S1. PRISMA flow-chart.

Table 1. Descriptive characteristics of the studies included.

Author, year	Country	N	N of diabetics at follow up	Mean age (SD)	Percentage of females	Serum 25OHD (SD) (nmol/L)	Follow- up (years)	Methods of assessment of serum 25OHD	Diagnostic criteria for diabetes	Type of covariates	Number of covariates	eNOS
Bolland A J et al, 2010	New Zealand	1471	29	74.0	100	50.9 (19.1)	5	RIA (DiaSorin, Stillwater, MN, USA)	Self- reported with a final adjudication by a specialist	Treatment allocation, age, body weight, smoking status.	4	5
Kositsawat J et al, 2014	USA	2193	477	74.6 (2.9)	52	65.8 (28.8)	2	RIA (DiaSorin, Stillwater, MN, USA)	Abnormal HbA1c ($\geq 6.5\%$)	Age, sex, recruitment site, BMI, physical activity, vitamin D	11	5

Table 1. Descriptive characteristics of the studies included.

Author, year	Country	N	N of diabetes at follow up	Mean age (SD)	Percentage of females	Serum 25OHD (SD) (nmol/L)	Follow- up (years)	Methods of assessment of serum 25OHD	Diagnostic criteria for diabetes	Type of covariates	Number of covariates	eNOS
										supplementation, multivitaminic use, season, PTH, race, diabetes status at follow-up.		
Napoli N et al, 2016	USA	1939	139	73.3 (5.7)	0	65.25 (20.8)	6.4	Liquid chromatogra- phy tandem mass	FPG ≥ 126 mg/dl, self- reported	Age, site, race, season, BMI, calcium intake	6	7

Table 1. Descriptive characteristics of the studies included.

Author, year	Country	N	N of diabetics at follow up	Mean age (SD)	Percentage of females	Serum 25OHD (SD) (nmol/L)	Follow- up (years)	Methods of assessment of serum 25OHD	Diagnostic criteria for diabetes	Type of covariates	Number of covariates	eNOS
								spectrometry (thermofisher Scientific, franklin, MA, USA)				
Pilz S et al, 2012	Netherlands	351	45	67.8 (5.7)	61	56.7 (18.8)	7.5	RIA (DiaSorin, Stillwater, MN, USA)	FPG ≥ 126 mg/dl	Fasting glucose, age, sex, BMI, HDL, TG, hypertension, physical activity level,	11	7

Table 1. Descriptive characteristics of the studies included.

Author, year	Country	N	N of diabetes at follow up	Mean age (SD)	Percentage of females	Serum 25OHD (SD) (nmol/L)	Follow- up (years)	Methods of assessment of serum 25OHD	Diagnostic criteria for diabetes	Type of covariates	Number of covariates	eNOS
										season, PTH, eGFR		
Robinson G et al, 2011	USA	5140	317	66.0	100		7.3	DiasORIN liaison CHEMILU MINESCEN CE METHOD (DiaSorin, Stillwater, MN)	Self - reported, drugs	Age, ethnicity, latitude, season, WHI study indicators, BMI, hypertension, fiber intake, magnesium intake, physical	10	7

Table 1. Descriptive characteristics of the studies included.

Author, year	Country	N	N of diabetes at follow up	Mean age (SD)	Percentage of females	Serum 25OHD (SD) (nmol/L)	Follow- up (years)	Methods of assessment of serum 25OHD	Diagnostic criteria for diabetes	Type of covariates	Number of covariates	eNOS
										activity level		
Schafer AL et al, 2014	USA	5463	320	76.5	100	57.4 (27.2)	8.6	liquid chromatogra phy tandem mass spectrometry (thermofishe r Scientific, franklin, MA, USA)	Self - reported	Age, clinic site, BMI, hypertension, self-reported health	5	6
Shottker B	Germany	7791	829	62.0	58	46.1	8	RIA	HbA1c \geq	Age, sex,	15	8

Table 1. Descriptive characteristics of the studies included.

Author, year	Country	N	N of diabetes at follow up	Mean age (SD)	Percentage of females	Serum 25OHD (SD) (nmol/L)	Follow- up (years)	Methods of assessment of serum 25OHD	Diagnostic criteria for diabetes	Type of covariates	Number of covariates	eNOS
et al, 2012				(3.3)		(9.2)		(DiaSorin, Stillwater, MN, USA)	6.5%	season, multivitamin supplementatio n, frequent fish consumption, BMI, HbA1c, family history of diabetes, education, physical activity,		

Table 1. Descriptive characteristics of the studies included.

Author, year	Country	N	N of diabetes at follow up	Mean age (SD)	Percentage of females	Serum 25OHD (SD) (nmol/L)	Follow- up (years)	Methods of assessment of serum 25OHD	Diagnostic criteria for diabetes	Type of covariates	Number of covariates	eNOS
										smoking, hypertension, renal dysfunction, CRP, fasting TG		
Thorand B et al,2011	Germany	1683	416	NA	47		11	Enzyme immunoassay IDA, Frankfurt, Germany	Self- reported	Age, sex, survey, season, BMI, smoking, alcohol use, physical	17	6

Table 1. Descriptive characteristics of the studies included.

Author, year	Country	N	N of diabetes at follow up	Mean age (SD)	Percentage of females	Serum 25OHD (SD) (nmol/L)	Follow- up (years)	Methods of assessment of serum 25OHD	Diagnostic criteria for diabetes	Type of covariates	Number of covariates	eNOS
										activity, systolic BP, total cholesterol/HD L, family history of diabetes, CRP, IL6, ICAM-1, IFN-alpha inducible protein,		

Table 1. Descriptive characteristics of the studies included.

Author, year	Country	N	N of diabetes at follow up	Mean age (SD)	Percentage of females	Serum 25OHD (SD) (nmol/L)	Follow- up (years)	Methods of assessment of serum 25OHD	Diagnostic criteria for diabetes	Type of covariates	Number of covariates	eNOS
										markers of inflammation, waist to hip ratio.		
Veronese N et al, 2014	Italy	2227	291	76.1 (7.8)	59	80.1 (54.7)	4.4	RIA (DiaSorin, Stillwater, MN, USA)	FPG \geq 126 mg/dl or HbA1c \geq 6.5% or use of medication s	Age, gender, waist, hypertension, education, monthly income, smoking,	11	8

Table 1. Descriptive characteristics of the studies included.

Author, year	Country	N	N of diabet s at follow up	Mean age (SD)	Percentage of females	Serum 25OHD (SD) (nmol/L)	Follow- up (years)	Methods of assessment of serum 25OHD	Diagnostic criteria for diabetes	Type of covariates	Number of covariates	eNOS
										eGFR, FPG, HbA1c, total cholesterol		
Total (weighted for the sample size)		28,258	2,863	67.7 (4.3)	64%	56.8 (22.4)	Median =7.3 (range: 2-11) years	5 studies: RIA; 2 studies: mass spectrometr y; 1 study: ELISA; 1 study:			Median=11 (range: 4-17)	Media n=7 (range : 5-9)

Table 1. Descriptive characteristics of the studies included.

Author, year	Country	N	N of diabet s at follow up	Mean age (SD)	Percentage of females	Serum 25OHD (SD) (nmol/L)	Follow- up (years)	Methods of assessment of serum 25OHD	Diagnostic criteria for diabetes	Type of covariates	Number of covariates	eNOS
								chemilumin escence				

Abbreviations: SD = standard deviation, 25OHD = 25-Hydroxyvitamin D, RIA = radioimmunoassay, HbA1c = glycated hemoglobin, BMI = body mass index, PTH = parathyroid hormone, FPG = fasting plasma glucose, HDL = high-density lipoproteins, TG = triglyceride, eGFR = glomerular filtration rate, CRP = C-reactive protein, Systolic BP = systolic blood pressure (BP), IL6 = Interleukin 6, ICAM 1 = Intercellular Adhesion Molecule 1, IFN-alpha = interferons-alpha, ELISA = enzyme-linked immunosorbent assay.